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A cut-off serum creatinine value of 1.5 mg/dl for AKI – To be or not to be

To the Editor:

Acute renal failure (ARF) is a common problem in patients with decompensated cirrhosis and ascites [1]. Traditionally, the diagnosis of ARF is made using the conventional criteria of a 50% increase in serum creatinine with the final serum creatinine reaching $\geqslant$1.5 mg/dl [2]. More recently, it has been recognized in non-cirrhotic patients that smaller increases in serum creatinine also have a negative impact on survival [3]. This has led various learned societies to re-define ARF as acute kidney injury (AKI), incorporating even small changes in serum creatinine either in absolute or percentage terms in the diagnostic criteria [4–6]. The degree of AKI severity is also defined by stages [4–6]. The most commonly reported classification used to diagnose AKI is that of the Acute Kidney Injury Network (AKIN), which set forth specific serum creatinine and urine output changes to define stages of AKI, without setting a fixed serum creatinine level in its diagnostic criteria [5]. Comparison of results from various studies in patients with cirrhosis has been difficult, as these studies assessed cirrhotic patients of various disease severities, in different hospital settings, using different methodologies to calculate the change in serum creatinine [7–9]. Emerging from these studies are the findings that both the severity of AKI, as well as the progression of AKI have a negative impact on patient survival. In two recent articles by Fagundes *et al.* [10], and Piano *et al.* [11], published in the *Journal of Hepatology*, which evaluated the impact of AKI on short-term mortality in patients with decompensated cirrhosis, admitted to the hospital for various reasons, similar trends were reported. Both studies incorporated parts of the AKIN criteria using the conventional criteria for the diagnosis of AKI. Fagundes *et al.* found that patients with stage 1 AKI (increase in serum creatinine by either 0.3 mg/dl or by 50% irrespective of the final serum creatinine) and peak serum creatinine of $\leqslant$1.5 mg/dl had a very good survival, similar to that of non-AKI patients [10]. Piano *et al.* found that the conventional diagnostic criteria, using a cut-off serum creatinine of 1.5 mg/dl was better than the AKIN criteria in the prediction of survival. This is not surprising, as the conventional diagnostic criteria tend to select out patients with more severe kidney injury. Furthermore, a serum creatinine of $\geqslant$1.5 mg/dl was able to predict progression of AKI [11]. Based on these two studies, Fagundes *et al.* proposed instituting a new classification of AKI in cirrhosis, separating cirrhotic patients with AKI into 3 subgroups: (i) stage 1 with a final serum creatinine of $\leqslant$1.5 mg/dl, (ii) stage 1 with a final serum creatinine of >1.5 mg/dl, and (iii) combined stages 2 and 3. Piano *et al.* suggested that future interventional trials should incorporate certain aspects of the AKIN criteria, namely, small increment of 0.3 mg/dl in serum creatinine and staging, to allow assessment of progression, while maintaining the conventional diagnostic criteria, requiring a minimum serum creatinine of $\geqslant$1.5 mg/dl.

Therefore, these two studies seem to suggest a serum creatinine cut-off value of 1.5 mg/dl is important in the management of AKI and the prediction of patient outcome in cirrhosis. These studies also imply that AKI episodes with a lower peak serum creatinine may not be clinically important., and may not require intervention However, as Thalheimer and Burroughs pointed out, AKI with a peak serum creatinine of <1.5 mg/dl is not a benign condition [12]. One has to emphasize that the above two studies were designed specifically to evaluate the impact of AKI on short-term survival in a very specific population of cirrhotic patients, namely hospitalized cirrhotic patients. They did not set out to evaluate the impact of AKI on other events that could be important in the natural history of cirrhosis, such as recurrence of AKI, the development of future complications, or future hospitalizations. In light of the marked variation in baseline creatinine between cirrhotic patients, using a specific serum creatinine cut-off value could potentially result in the late diagnosis of AKI, and delay interventions. In a totally different setting of outpatient decompensated cirrhotics, Tsien *et al.* reported that patients with AKI, defined as a rise in serum creatinine by either 0.3 mg/dl within <48 h or an increase of 50% from a stable value in the previous 6 months, and a mean peak serum creatinine within the normal laboratory range had a worse prognosis compared to those without AKI when followed for 12 months [13]. In another cohort of hospitalized decompensated cirrhotic patients with infection (n = 337) [14], a higher percentage of those who developed AKI (n = 166) died within 30 days, despite receiving the standard of care for their AKI plus prompt antibiotic treatment. Re-analysis of the data showed that of the 166 patients who developed AKI, there were 31 patients whose peak serum creatinine was $\leqslant$1.5 mg/dl (group A), and 135 patients whose

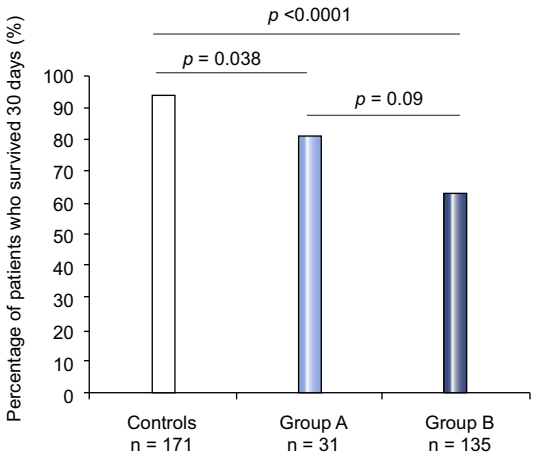

Fig. 1. Patient survival. Percentage of patients who survived more than 30 days amongst cirrhotic patients with infection, and who did not develop acute kidney injury (Group A), who developed acute kidney injury but the peak serum creatinine remained 61.5 mg/dl (Group B), and who developed acute kidney injury but the peak serum creatinine was >1.5 mg/dl (Group C).

peak serum creatinine was >1.5 mg/dl (group B). 81% of group A patients survived 30 days *vs.* 93% of control subjects, $p = 0.038$ (Fisher's exact test) (Fig. 1). Interestingly, the 30 day survival of group B (63%) was statistically similar to that of group A ($p = 0.09$) despite group B having significantly more organ failures (group A: median number of organ failure = 1, interquartile range 0:1; group B: median number of organ failure = 1, interquartile range 1:2) ($p = 0.008$, Mann-Whitney *U* test). Therefore, in different clinical settings to those of Fagundes *et al.*, and Piano *et al.*, using the conventional criteria of serum creatinine of $\geqslant$1.5 mg/dl to diagnose AKI may lead to clinical decisions that could be detrimental to these patients.

The diagnosis of AKI in cirrhosis is currently still a matter under discussion. We have borrowed the AKIN criteria from nephrologists [5], but do not really adhere strictly to the diagnostic criteria of AKIN for the diagnosis of AKI, as no study to date has incorporated the urine output criteria of the AKIN definition. This is reasonable because cirrhotic patients have issues that are particular to themselves, such as lower urine output even without AKI, due to avid sodium and water retention. Cirrhotic patients also have malnutrition, leading to lower muscle mass, thereby artificially lowering the serum creatinine [15]. This is particularly problematic in female patients, whose serum creatinine significantly overestimates renal function; utilization of a 1.5 mg/dl cut-off for diagnosing clinically significant AKI may discriminate against women [16]. Therefore, academic societies are working together to try to identify the best unified diagnostic criteria for AKI in cirrhosis. Although Fagundes *et al.* and Piano *et al.* have provided robust results for their particular sets of patients, their results may not be generalizable and equitable to other patients with cirrhosis. Therefore, to use results of selected individual studies to propose widespread changes in diagnostic criteria for AKI may be premature. Rather, these studies should stimulate the performance of prospective trials that will clarify the best timing to initiate therapy for renal dysfunction that will prevent its progression, thereby improving the survival of this fragile population of patients with decompensated cirrhosis.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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On behalf of the North American Consortium for the Study of End-Stage Liver Disease

Reply to: "A cut-off serum creatinine value of 1.5 mg/dl for AKI – To be or not to be"

To the Editor

We really appreciate the interest of Wong and colleagues, from the North American Consortium in the Study of End-Stage Liver Disease (NACSELD) group, on our study published in the *Journal of Hepatology* in late 2013 [1]. As a research group interested in kidney dysfunction in cirrhosis, we share the concerns of our American colleagues about improving the diagnosis and management of kidney dysfunction in cirrhosis. Needless to say, we agree on their comments about the need for improving the interpretation of the relationship between glomerular filtration rate and serum creatinine values in women. This is particularly important in the application of the MELD score for organ allocation in liver transplantation. We would be willing to join efforts with our American colleagues to further investigate this issue. That said, we would like to highlight 4 important issues related to their letter:

(1) The study of Fagundes *et al.* [1] was a prospective evaluation of all patients requiring hospital admission for an acute decompensation of cirrhosis, during a 26-month period, with the only exceptions of patients with large hepatocellular carcinoma, previous solid organ transplantation, and those on renal replacement therapy. Therefore, our study population included "all comers" to a tertiary hospital. We do not know whether our results apply to similar populations of patients with cirrhosis in other tertiary hospitals or to different populations in other settings. The new classification proposed (categorizing AKI stage 1 in two subgroups-A and B- and combining stages 2 and 3) was internally validated, but we obviously stated in the manuscript that it would require external validation in future studies before it could be widely applicable. Nonetheless, it is important to remark that in the same issue of the *Journal*, in which our study was published, Piano *et al.* reported amazingly similar results in a population of "all comers" with decompensated cirrhosis, in a tertiary hospital in Northern Italy [2].

(2) Wong *et al.* disapprove of our proposal for this modified AKI classification that uses the cut-off value of serum creatinine of 1.5 mg/dl, to categorize patients with AKI stage 1. In our opinion, as well as that of others, the use of a cut-off of serum creatinine makes perfect pathophysiological sense because it helps put into perspective the relative increase in serum creatinine used in the AKIN classification. In this regard, it is clear that a 50% increase in serum creatinine is markedly dependent on the baseline creatinine value. In fact, a 50% increase does not have the same significance in a patient with a baseline serum creatinine level of 0.6 mg/dl, compared to that of a patient with a baseline level of 1.2 mg/dl. In the first case, the final value is 0.9 mg/dl, which despite the 50% raise still represents a relatively preserved glomerular filtration rate. By contrast, in the second case the final value is 1.8 mg/dl, which corresponds to a very low glomerular filtration rate, indicating the presence of significant organ failure. If we translate this example to the liver using serum bilirubin as marker of liver function, it is clear that a 50% increase in serum bilirubin does not represent the same degree of liver failure when the final value of bilirubin is 3 mg/dl or 12 mg/dl.

(3) Another argument used by Wong *et al.* to refute our classification based on a cut-off level of serum creatinine of 1.5 mg/dl, is that it could result in late diagnosis of AKI and delayed interventions. We disagree with this interpretation of our findings. Nowhere in our study it is stated that patients with AKI stage 1A should not be treated for AKI. In fact, all patients diagnosed at AKI stage 1A (serum creatinine <1.5 mg/dl) were investigated to determine the cause of AKI and received immediate treatment, whenever a cause of AKI was identified. Moreover, with our approach, the majority of patients (77%) were diagnosed at AKI stage 1, while only 12% were diagnosed at stage 3, which clearly seems to indi-